Spatio-temporal regulation of the formation of the somatosensory system

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Key words

Somatosensory system, barrel, barrel nets, birth, serotonin

Running title

Mechanisms of somatosensory development

Abstract

The somatosensory system in the brain has been widely used for investigating the mechanisms underlying neural circuit formation and developmental neural plasticity. In the primary somatosensory cortex (S1) of rodents, there are discrete cytoarchitectonic units called barrels. Reverse genetic analyses using knockout mice have revealed molecules that control spatial pattern formation of barrels in S1. Glutamatergic receptors such as the NMDA receptor and mGluR5, and molecules related to serotonin such as serotonin transporter and monoamine oxidase A are essential for the formation of barrels. In addition to the mechanisms of spatial pattern formation, those regulating the timing of developmental processes were uncovered recently. Barrels are formed soon after the birth of newborn mouse pups from their mothers, and it was shown that the timing of barrel formation was determined by the timing of the birth of mouse pups. The mechanisms downstream of birth were also examined. It would be intriguing to examine if the mechanisms found using the somatosensory system are applicable to other brain regions.

Introduction

The brain is the most complex and sophisticated organ in our body. In order to exhibit higher brain functions, it is essential to form neural circuits in the brain correctly during development. Therefore, elucidating the mechanisms underlying the formation of the brain during development and their abnormalities that cause brain diseases is an important issue. In this review, I will outline recent advances in our understanding of the mechanisms underlying the formation of the brain using the somatosensory system.

Characteristics of the sensory system

Sensory systems in the brain, such as the somatosensory system and the visual system, have been used for investigating the mechanisms underlying the formation of the brain. This is because the sensory system has several important advantages described below. First, the sensory system is useful for dissecting the roles of genetic factors and environmental factors in the formation of the brain. Using the sensory system, it is easy to manipulate environmental factors selectively. For example, in order to block visual inputs, what we have to do is only to place animals in darkness. Changing the balance of visual inputs from the two eyes can be achieved by suturing the eyelid of one eye. It is possible to study the effects of deprivation of one sensory modality such as vision on the other sensory systems such as the olfactory system. In the case of the somatosensory system, it is possible to operate sensory inputs by removing whiskers on the snout.

The second advantage is that the sensory system is suitable for investigating the mechanisms of developmental neural plasticity. The sensory system shows functional and structural neural plasticity in response to the changes of sensory inputs

from the outside world. Because sensory inputs are easy to manipulate, neural plasticity can be elicited relatively easily in the sensory system. Whisker lesion-induced barrel structural plasticity in the somatosensory cortex, ocular dominance plasticity in the visual cortex and eye-specific axon segregation in the lateral geniculate nucleus (LGN) are commonly used for investigating developmental neural plasticity.

The third advantage is that the sensory system is suitable for the study of the critical period. Developmental neural plasticity is observed only in a certain time period during development. This time period is called the critical period or the sensitive period. The mechanisms of the initiation and the termination of the critical period have been the subject of intense ongoing investigation, and the sensory system occupies important positions in the studies of brain formation during development.

The basic structures and developmental processes of the somatosensory system

The somatosensory system of rodents has been widely used for investigating the mechanisms of neural circuit formation during development (Erzurumlu & Gaspar, 2012, Lopez-Bendito & Molnar, 2003). Tactile information detected by whiskers on the snout is transmitted first to the trigeminal ganglion, then to the trigeminal nucleus in the brainstem, followed by the ventral posteromedial nucleus (VPM) in the thalamus, and then to the primary somatosensory cortex (S1) (Figure 1A). Because rodents rely largely on the somatosensory information from whiskers, the somatosensory cortex corresponding to whiskers occupies a large area in S1.

The somatosensory cortex of rodents is characterized by the presence of the somatosensory map, which reflects the distribution patterns of whiskers on the snout. The somatosensory maps corresponding to whiskers are called barrelettes in the

trigeminal nucleus, barreloids in the VPM, and barrels in S1 (Figure 1B). Barrels in S1 are cytoarchitectonic patterns of layer 4 neurons (Figure 1C). Neurons within a single barrel are considered to receive sensory inputs only from one corresponding whisker (Figure 1D). Within the barrel, thalamocortical axons derived from the VPM of the thalamus are distributed, making whisker-related patterns (Figure 1C). Barrels in S1 can be visualized by NeuN immunostaining, which reveals distribution patterns of neurons. In addition, whisker-related patterns of thalamocortical axons can be revealed with VGluT2 immunostaining and serotonin transporter (5-HTT) immunostaining. Cytochrome oxidase (CO) staining is also useful to demonstrate the patterning of barrels. Because barrels can be visualized easily, they are often used by many researchers.

The areas between barrels in layer 4 of S1 are called septa, and are believed to receive distinct sensory information. Barrels receive inputs from the VPM of the thalamus, while septa receive inputs from the posterior medial nucleus (POm). Although both barrels and septa are found in the somatosensory system, they transmit the information of different modalities. While barrels receive tactile information from whiskers, neurons in septa react to the rhythmic movement of whiskers. Septa are believed to monitor the movement of whiskers.

Although detailed studies about the somatosensory system from the periphery to layer 4 of S1 have been extensively performed, neuronal circuits within S1, which are involved in actual information processing, are not fully understood. To examine the neuronal circuits in S1, we selectively expressed GFP in layer 2/3 neurons of mouse S1 by using *in utero* electroporation, and analyzed the axonal trajectories of layer 2/3 neurons. We found that GFP-positive axons of layer 2/3 neurons were preferentially

distributed in septa of layer 4, and named this axonal projection pattern "barrel nets" (Figure 2) (Sehara *et al.*, 2010, Sehara *et al.*, 2012). Interestingly, when mCherry and synaptophysin-GFP were co-expressed in layer 2/3 neurons, GFP-positive puncta were found in barrel nets, suggesting that there are synapses on barrel nets and that barrel nets are functionally involved in information processing. It seems plausible that barrel nets are linking the information related to barrels and the information related to septa. The biological roles of barrel nets would be intriguing to investigate in the near future.

The developmental processes of the somatosensory system have also been studied in detail. Early in development, whisker-related patterns are not formed in the trigeminal nucleus, the VPM and S1 (Figure 3), and then whisker-related patterns appear sequentially from the periphery to the center within a largely overlapping but strictly ordered time period. Thalamocortical axons initially project to multiple barrels and eventually project to one barrel. Layer 4 neurons are distributed uniformly before barrel formation and gradually translocate to make barrel walls.

Layer 4 neurons initially send their dendrites in all directions, and the dendrites become limited to the barrel center as barrel formation proceeds. Recently, it has become possible by using a two-photon microscope to observe the dynamic re-organization of the dendrites of layer 4 neurons in the brain of living newborn mice (Mizuno *et al.*, 2014). Dynamic re-organization processes, which include the extension and the elimination of dendrites, were observed *in vivo*. In NMDA receptor knockout mice, the directional preference of the dendrites was lost, and the dendrites were randomly distributed.

The spatial regulation of the formation of the somatosensory system

Because the developmental processes of barrels in the somatosensory cortex have been described in detail, barrels have been widely used for investigating the molecular mechanisms of the formation and re-organization of neuronal circuits (Figure 3) (Erzurumlu & Kind, 2001, Lopez-Bendito & Molnar, 2003, Rebsam & Gaspar, 2006, O'Leary *et al.*, 1994). It was reported that the formation of barrelettes in the brainstem was inhibited in NMDA receptor knockout mice. The CxNR1 knockout mice, in which the NMDA receptor NR1 subunit is eliminated in the cerebral cortex, showed abnormality in barrels, while barrelettes in the brainstem and barreloids in the thalamus appeared normal (Iwasato *et al.*, 2000). Cytoarchitectonic barrels in layer 4 were missing, and whisker-related patterns of thalamocortical axons were incomplete in CxNR1 knockout mice. Furthermore, the dendrites of layer 4 neurons, which normally project to the barrel center, had lost their preferential distribution in the barrel center in CxNR1 knockout mice. Similarly, barrel formation is inhibited in mGluR5 knockout mice (Hannan *et al.*, 2001). These results suggest that glutamatergic neurotransmission is essential for barrel formation. NeuroD2 and phospholipase β1 (PLCβ1) are thought to be molecules located downstream of glutamate receptors. NeuroD2 is a transcription factor induced by calcium, and barrel formation was inhibited in NeuroD2 knockout mice (Ince-Dunn *et al.*, 2006). It seems likely that NeuroD2 mediates the effects of calcium influx from the NMDA receptor during barrel formation. Abnormalities in barrels were also found in PLCβ1 knockout mice (Hannan *et al.*, 2001). It seems plausible that PLCβ1 works downstream of mGluR5. However, in order to clarify the entire picture of the molecular mechanisms of barrel formation, more detailed analyses would be required.

Serotonin is a neurotransmitter involved in barrel formation (Figure 3). In

mice deficient for monoamine oxidase A (MAOA), which degrades serotonin, barrel formation was impaired (Cases *et al.*, 1996). Whisker-related patterns of thalamocortical axons and cytoarchitectonic barrels in layer 4 were disrupted in MAOA knockout mice. These results indicate that increases in serotonin concentrations result in inhibition of barrel formation. Furthermore, barrel formation was also impaired in knockout mice for serotonin transporter (5-HTT), which reuptakes serotonin into cells, suggesting that increases in extracellular serotonin levels inhibit barrel formation (Persico *et al.*, 2001). Because the phenotypes of 5-HTT knockout mice were rescued by combining these mice with serotonin 1B receptor knockout mice, the increases in extracellular serotonin concentrations were detected, at least partially, by the serotonin 1B receptor (Salichon *et al.*, 2001). In addition, it is known that barrels are disrupted in mice deficient for adenylyl cyclase 1 (AC1). It seems plausible that increases in extracellular serotonin concentrations stimulate the serotonin 1B receptor, which then inhibits AC1, resulting in impaired barrel formation.

The mechanism of morphological development of dendrites of layer 4 neurons has been analyzed. BTB/POZ domain–containing 3 (Btbd3) is mainly expressed in the barrel center, and the BTB/POZ domain mediates protein interaction in a transcriptional repression complex by the recruitment of co-repressors. When the expression of Btbd3 was inhibited by shRNA, dendrites of layer 4 neurons, which extend toward the barrel center in normal mice, were distributed diffusely (Matsui *et al.*, 2013). When Btbd3 was strongly expressed in the visual cortex, monocular deprivation caused changes in dendrite morphology. These results show that Btbd3 is an important gene for re-organization of dendrites during development.

Recently, we studied the mechanisms of the formation of local neural circuits

in the cerebral cortex using barrel nets. As mentioned above, barrel nets can be visualized easily by expressing GFP in layer 2/3 neurons using *in utero* electroporation. We co-introduced GFP and candidate molecules that may control the formation of the barrel nets. We found that formation of barrel nets was inhibited when dominant-negative cadherin was introduced, suggesting that cadherin mediates barrel net formation (Wakimoto *et al.*, 2014). Cadherin seems to mediate the formation rather than the maintenance of barrel nets. This is because barrel nets were disrupted when dominant-negative cadherin was expressed early in development, while barrel nets were preserved if dominant-negative cadherin was expressed after barrel nets were formed. It was reported that cadherin mediates selective neural circuit formation in the midbrain and the hippocampus. However, the roles of cadherin in neural circuit formation in the cerebral cortex, which is the center of higher brain function, remain unclear. Our results suggest that cadherin is also important for local neuronal circuit formation in the cerebral cortex (Wakimoto *et al.*, 2014).

The temporal regulation of the formation of the somatosensory system

In order for a complete understanding of the mechanisms of brain formation, both spatial and temporal regulations must be understood. Although spatial regulations have been extensively investigated as mentioned above, the mechanisms of temporal regulation remain largely unknown. Particular developmental processes should occur at specific time points during development, and if this timing is disrupted, it can cause developmental abnormalities. Therefore, understanding the mechanisms of temporal regulation that define the timing of developmental processes is quite important.

To investigate these mechanisms, we analyzed the temporal regulation of

barrel formation in S1. Because barrels are formed soon after the birth of mouse pups, we hypothesized that birth itself is a trigger to start barrel formation. To test this hypothesis, we artificially induced preterm birth and examined when barrels are formed. We found that barrels were formed significantly earlier in preterm pups compared with full-term pups (Figure 4A) (Toda *et al.*, 2013). We also found that precocious barrel formation is due to earlier initiation of barrel formation rather than accelerated speed. These results suggest that the time of birth regulates the initiation of barrel formation (Figure 4B) (Toda *et al.*, 2013).

We further examined the molecular mechanisms that connect birth and barrel formation. It seemed possible that one of the molecules involved in the spatial regulation of barrel formation was rate-limiting for barrel formation and was actually located downstream of birth. Although previous studies showed that MAOA knockout mice, in which the extracellular concentration of serotonin was abnormally high, had disrupted barrels, the physiological roles of serotonin in barrel formation during normal development were unknown. We hypothesized that serotonin is located downstream of birth, and that serotonin controls the initiation of barrel formation (Figure 4). We measured serotonin concentrations in the cerebrospinal fluid (CSF) and in fact found that the serotonin concentration significantly decreased soon after birth (Toda *et al.*, 2013). We further found that serotonin concentrations were reduced earlier in preterm pups. These results suggest that birth causes a decrease in serotonin concentrations in the CSF. We next examined if the reduction of serotonin regulates the initiation of barrel formation. We inhibited serotonin synthesis using the tryptophan hydroxylase inhibitor PCPA, and found that barrel formation was accelerated. We also inhibited serotonin degradation and found that serotonin reduction is required for the effects of premature

birth on barrel formation. These results indicate that serotonin reduction is necessary and sufficient for the initiation of barrel formation by birth (Figure 4) (Toda *et al.*, 2013).

Because we found that birth regulates anatomical neural circuit formation as described above, we examined if birth also regulates functional development of animal behaviors. We focused on suckling behavior, which develops soon after birth. Sectioning the infraorbital nerve completely prevented pups from finding nipples, suggesting that suckling behavior requires somatosensory inputs from the snout. While it takes a relatively longer time for mouse pups to find the nipples of their mothers soon after birth, it becomes quicker as mouse pups develop. We examined if the development of suckling behavior is controlled by birth, and found that the development of suckling behavior in preterm pups was earlier than that of full-term pups. These results suggest that the functional development of suckling behavior is also controlled by birth (Toda & Kawasaki, 2014).

We also examined whether this regulatory mechanism downstream of birth also controls the formation of other neural circuits. Interestingly, as described above, we have found that serotonin levels are reduced in the CSF soon after birth. Because the CSF makes contact with various brain regions, the changes in serotonin concentrations in the CSF seemed like they would have an impact on various brain regions. We focused on eye-specific segregation of retinogeniculate axons in the LGN. As well as barrel formation, eye-specific segregation proceeds soon after birth, raising the possibility that eye-specific segregation is regulated by birth. In addition, consistent with barrel formation, eye-specific segregation is inhibited by increased serotonin in MAOA knockout mice. Retinal ganglion cells (RGCs) in the retina send their axons to the

lateral geniculate nucleus (LGN) of the thalamus. In adult mice, axons from the right and left eyes are distributed in distinct regions in the LGN, and are referred to as eye-specific axonal projections. In contrast, RGC axons from the two eyes are intermingled and not fully segregated in the LGN immediately after birth, but are segregated about 10 days after birth in mice. Consistent with the case of barrel formation, we found that eye-specific segregation of RGC axons was accelerated by preterm birth and by serotonin reduction (Toda *et al.*, 2013). These results indicate that the mechanism regulating the initiation of barrel formation also regulates neural circuit formation in the visual system (Figure 4). It would be intriguing to investigate if the mechanisms described here also control neural circuit formation in a variety of other brain regions.

The mechanisms of developmental neural plasticity and the critical period in the somatosensory system

The somatosensory system is also used for studying the mechanisms of developmental neural plasticity. In the rodent somatosensory cortex, plastic changes can be induced by cauterization of whisker follicles on the snout soon after birth (whisker lesion-induced barrel structural plasticity). In response to cauterization of whisker follicles, the barrels corresponding to the injured whiskers shrink, and the adjacent barrels expand. Recently, it was reported that whisker-lesion induced barrel structural plasticity was impaired in glutamate transporter 1 (GLT1) knockout mice, while barrel formation was normal (Takasaki *et al.*, 2008). Similarly, whisker lesion-induced barrel structural plasticity is prohibited in glutamate/aspartate transporter (GLAST) deficient mice (Takasaki *et al.*, 2008). These results suggest that glutamate transporters are necessary for plastic

changes in response to whisker follicle injury.

Using the somatosensory system, the mechanisms of the critical period can also be examined. Whisker-lesion induced barrel structural plasticity is observed within a short time period immediately after birth, and once this critical period has passed, the plastic changes cannot be induced. For example, whisker-lesion induced barrel structural plasticity can be elicited only in the first postnatal week in mice. The mechanisms regulating the end of the critical period have been attracting attention, and the possible roles of the neurotransmitter serotonin and glutamate have been examined. It was reported that the MAOA inhibitor clorgyline or MAOA knockout mouse did not affect when the critical period terminates (Rebsam *et al.*, 2005). Combining MAOA knockout mice and the serotonin synthesis inhibitor PCPA, the timing of barrel formation can be modified. The critical period was not affected in MAOA knockout mice with a 3-day delay in barrel formation. Similarly, CxNR1 knockout mice showed normal termination of the critical period (Datwani *et al.*, 2002). While cytoarchitectonic barrels were disrupted in CxNR1 knockout mice, whisker-related patterns of thalamocortical axons were formed. Using whisker-related patterns of thalamocortical axons, the critical period was found to be preserved. These results suggest that the end of the critical period is not determined by serotonin and glutamate.

It was reported that Nogo-A/B and the Nogo receptor, which inhibit axonal regeneration, regulated the end of the critical period in the visual cortex (McGee *et al.*, 2005), raising the possibility that Nogo-A/B and the Nogo receptor are also involved in the end of the critical period in the somatosensory system. Because, in addition to Nogo-A/B, MAG and OMgp were reported to mediate the inhibition of axon regeneration, we utilized Olig1 knockout mice, in which most oligodendrocytes are

eliminated. Because Nogo-A/B, MAG and OMgp are all expressed in oligodendrocytes, elimination of oligodendrocytes leads to the removal of Nogo-A/B, MAG and OMgp. Interestingly, mice deficient for Olig1 did not affect the time of the critical period (Toda *et al.*, 2008). This result suggests that oligodendrocytes are dispensable for the end of critical period in the somatosensory system, and that the mechanisms determining the end of critical periods are different between the somatosensory system and the visual system (Toda *et al.*, 2008). It should be noted that because a recent report showed that chondroitin sulfate proteoglycans (CSPG), which is expressed in astrocytes, binds to the Nogo receptor, it remains possible that the Nogo receptor mediates the termination of the critical period.

Conclusion

In this review, I've introduced recent research about the mechanisms underlying the development of the somatosensory system. The somatosensory system has been widely used for studying developmental plasticity, the critical period, and spatial and temporal control of circuit formation. It would be intriguing to examine if the findings obtained using the somatosensory system are also applicable to other brain regions. Understanding the diversity and commonality of mechanisms among various brain regions is an important goal for future research.

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Figure Legends

Figure 1. Schematic views of the somatosensory system

A. Tactile information detected by whiskers is transferred first to the trigeminal nucleus in the brainstem, then to VPM in the thalamus and eventually to the primary somatosensory cortex (S1).

B. Somatosensory maps in the somatosensory system. Somatosensory maps corresponding to the distribution of whiskers are present in the somatosensory system. The barrelette, barreloid and barrel receiving tactile information from the red whisker are shown in red.

C. The structure of barrels in the primary somatosensory cortex. A cross-sectional view of the cerebral cortex is shown. Cytoarchitectonic barrels of layer 4 neurons are shown in red. Thalamocortical axons derived from the VPM of the thalamus are distributed within barrels.

D. Information from one whisker is mainly transferred to one corresponding barrel.

Figure 2. The structure of barrel nets

A. A coronal view of the primary somatosensory cortex. Layer 2/3 neurons send axons preferentially to septa in layer 4.

B. A tangential view of the primary somatosensory cortex at the level of layer 4. The distribution pattern of the axons of layer 2/3 neurons is shown in green.

Figure 3. Molecules required for spatial pattern formation of barrels

Figure 4. Birth regulates the initiation of barrel formation through serotonin signaling

A. When mouse pups are born earlier than the due date, extracellular serotonin levels decrease earlier, and as a result, barrels are formed earlier in preterm pups compared with full-term pups. The horizontal axis indicates time after fertilization.

B. Birth induces the reduction of extracellular serotonin, and as a result, barrel formation in S1 (left) and eye-specific segregation of RGC axons in the LGN (right) proceed. Red and green represent RGC axons derived from the ipsilateral and contralateral eyes, respectively. Yellow represents regions containing both ipsilateral and contralateral RGC axons.

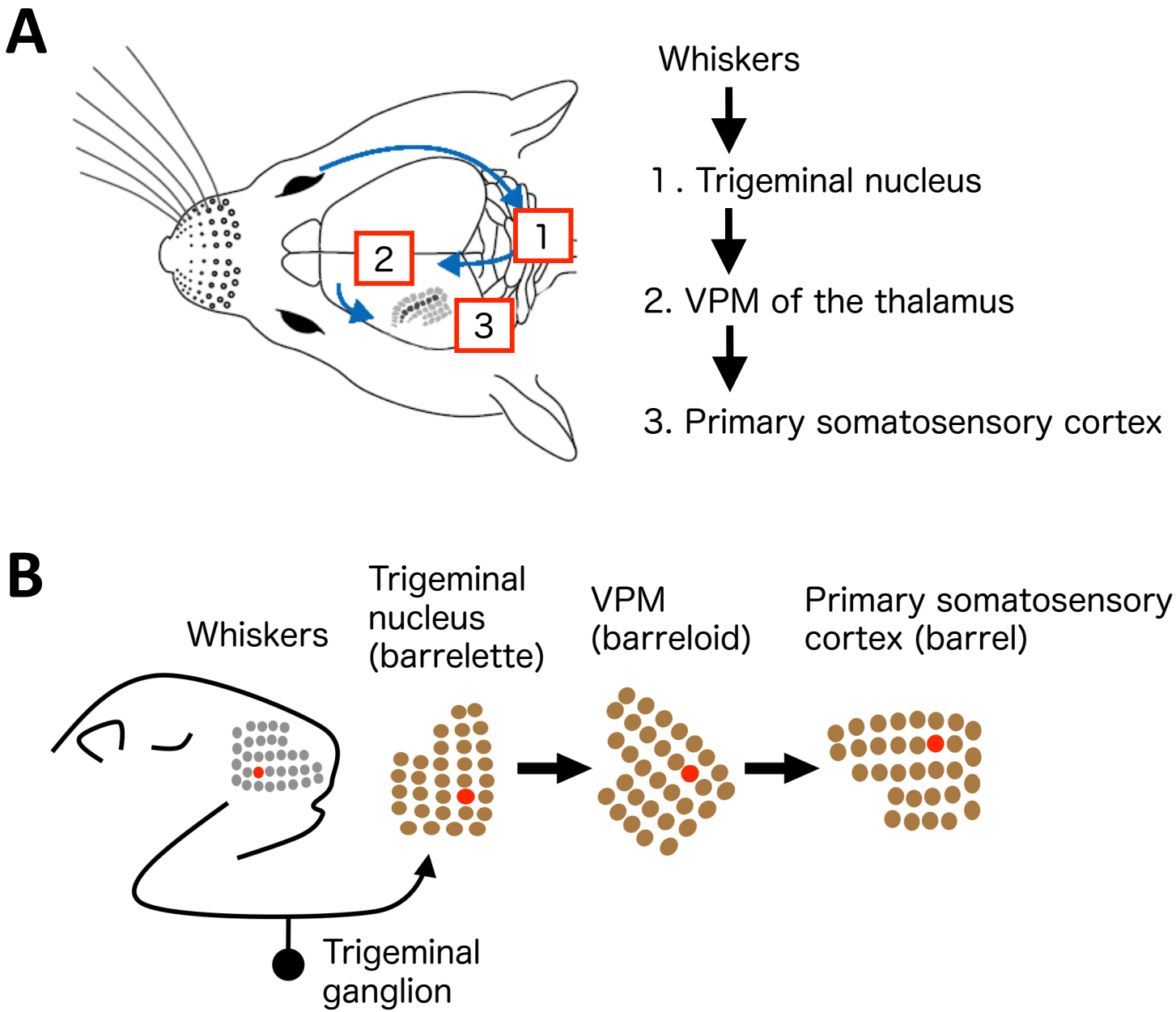
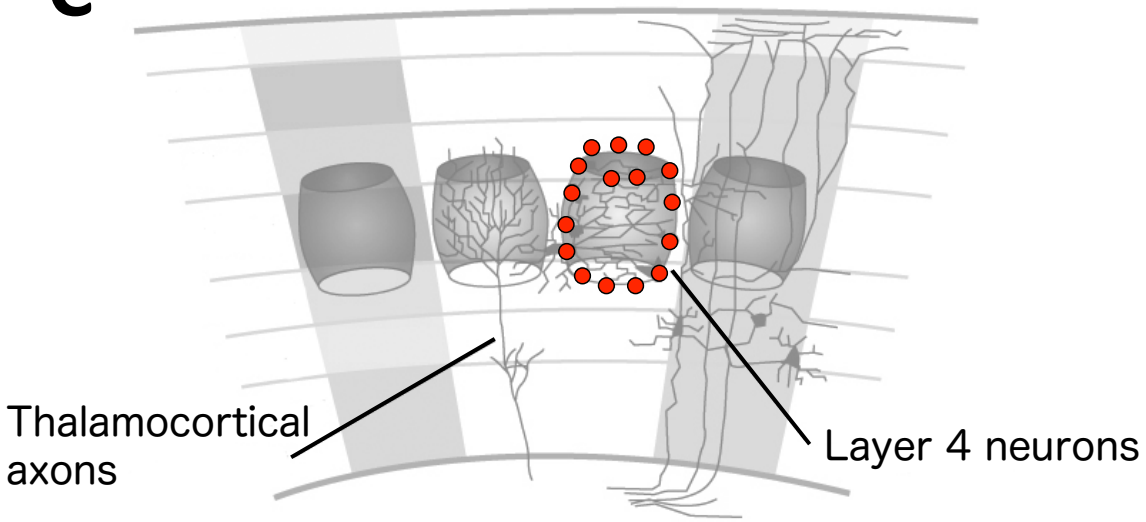

A
1
2
3
Whiskers
1 . Trigeminal nucleus
2. VPM of the thalamus
3. Primary somatosensory cortex
B
Whiskers
Trigeminal nucleus (barrelette)
VPM (barreloid)
Primary somatosensory cortex (barrel)
Trigeminal ganglion

Figure 1

C


Thalamocortical
axons
Layer 4 neurons

D

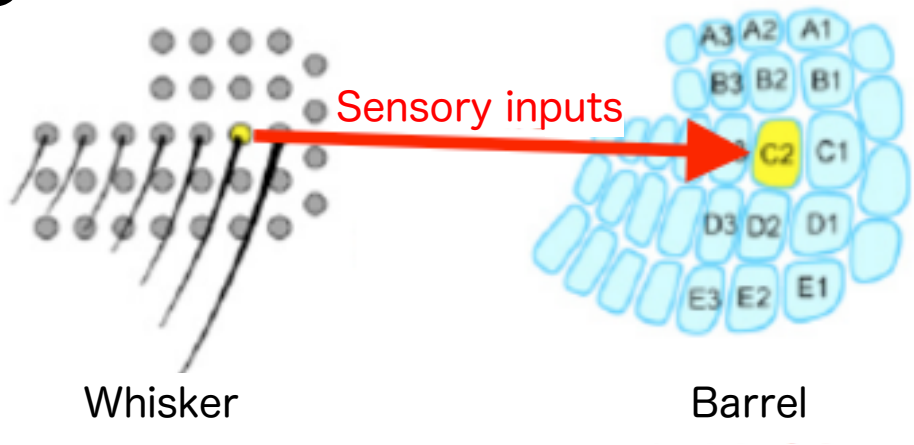

Sensory inputs
A3
A2
A1
B3
B2
B1
C2
C1
D3
D2
D1
E3
E2
E1
Whisker
Barrel

Figure 1

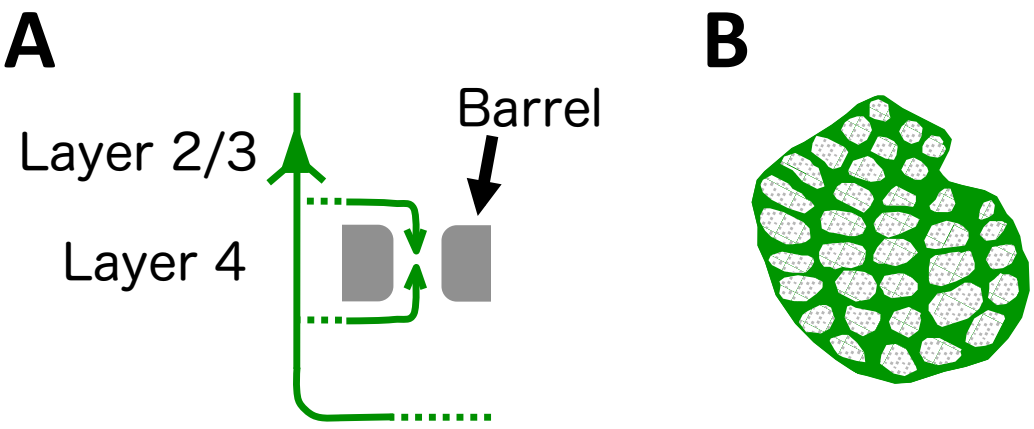


Figure 2

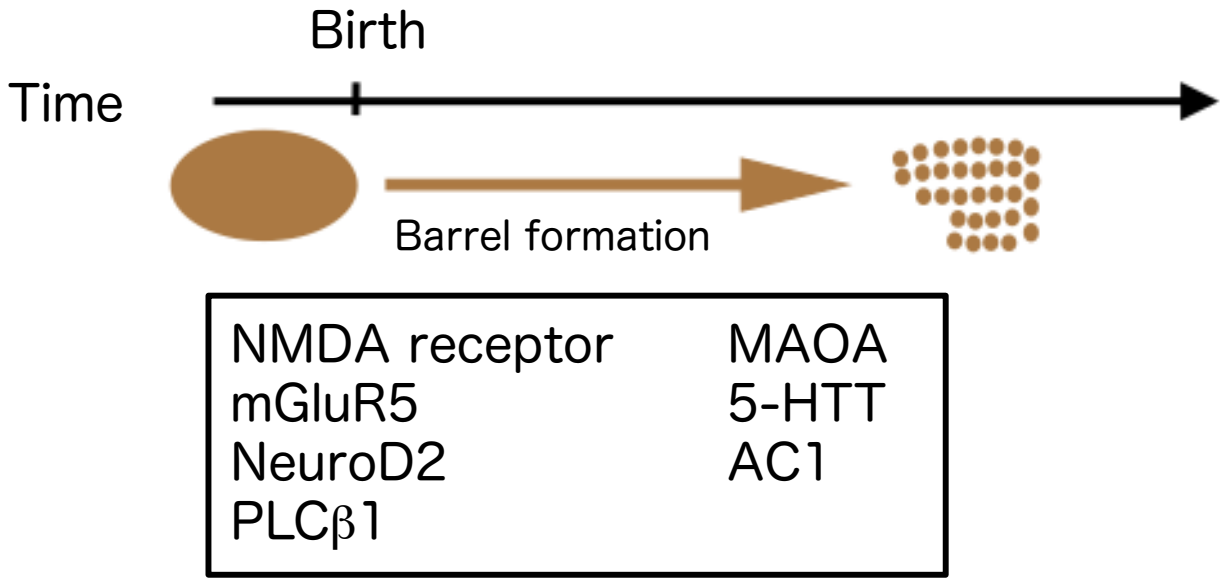

Birth
Time
Barrel formation
NMDA receptor
mGluR5
NeuroD2
PLCβ1
MAOA
5-HTT
AC1

Figure 3

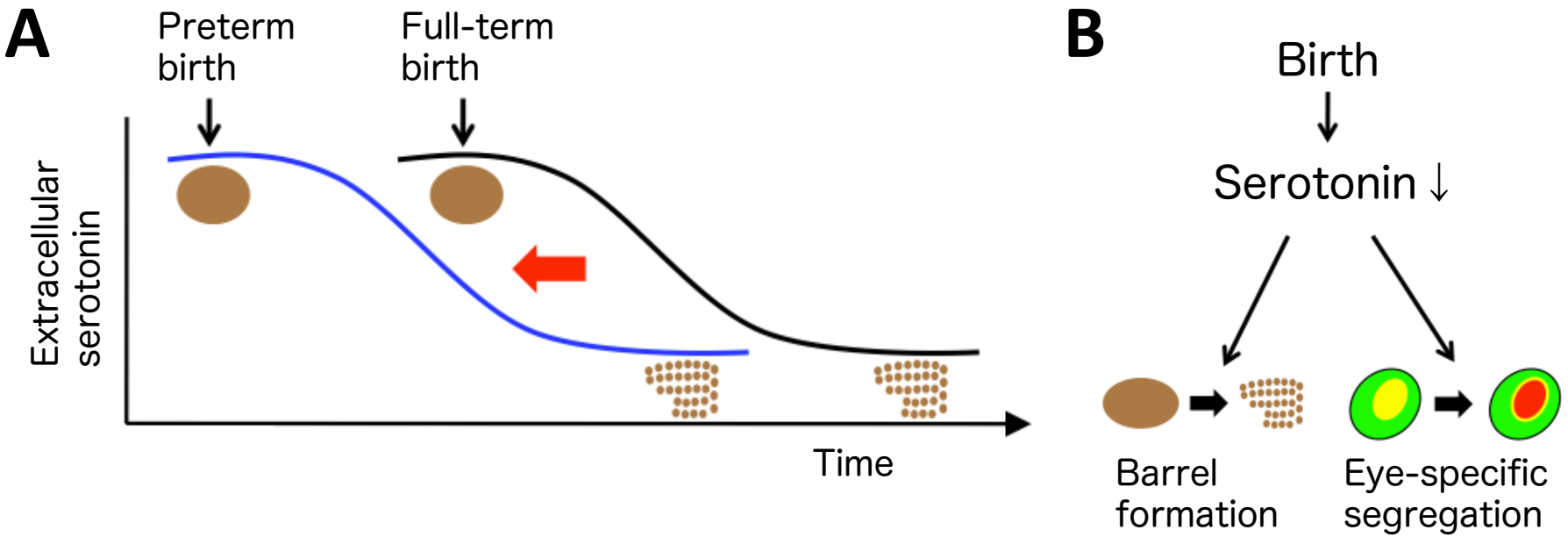

A
Preterm birth
Full-term birth
Extracellular serotonin
Time
B
Birth
Serotonin ↓
Barrel formation
Eye-specific segregation

Figure 4